REMARKS/ARGUMENTS

Reconsideration of this application is respectfully requested.

The withdrawal of the rejection of the claims as anticipated by Amalfitano et al is noted with appreciation.

Claims 1, 2, 8-11, 18, 21, 22 and 24-29 stand rejected under 35 USC 102(b) as allegedly being anticipated by Van Bree et al. The rejection is traversed.

Claim 1 (from which the other claims subject to this rejection depend) relates to a nucleic acid encoding a chimeric polypeptide comprising a secretory signal sequence operably linked to human GAA. Claim 1 requires that the secretory signal sequence replace the leader sequence of native human GAA. It is submitted that Van Bree et al includes no such teaching.

A rejection under 35 USC 102 is proper only when the subject matter of the claims is identically disclosed/described in the cited art.

> Thus, it is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention. See Arkley, 455 F.2d at 587 ("[T]he [prior art] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.").
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> Net MoneyIn, Inc. v. VeriSign, Inc., 545 F.3d 1359, 1371 (Fed Cir. 2008)

Applicants respectfully submit that Van Bree et al does not "clearly and unequivocally" disclose the claimed invention (or direct an artisan to it) "without any need for picking, choosing and combining various disclosures not directly related to each other by the teachings of the cited reference".

On the contrary, the Examiner relies on general teachings in Van Bree et al relating to lysosomal protein processing (page 7, lines 26-32), teachings relating to selection of a signal sequence capable of directing secretion of a lysosomal protein (page 9, lines 16-30), and a teaching of the replacement of the secretion signal sequence linked to the lysosomal protein coding sequence with a signal sequence that targets the processing enzyme to the endoplasmic reticulum without secretion (page 11, lines 29-35). The Examples provided in Van Bree et al make reference to the human acid α glucosidase gene. However, no reference is found in those Examples (or elsewhere in Van Bree et al) to a nucleic acid encoding a chimeric polypeptide comprising a secretory signal sequence operably linked to human acid α-glucosidase (GAA) wherein that secretory signal sequence replaces the leader sequence of the native human GAA, as required by the claims.

As the citation does "clearly and unequivocally" disclose the invention, withdrawal of the rejection is clearly in order and same is requested.

Claims 5, 12, 14-16, 73, 75 and 80-82 stand rejected under 35 USC 103 as allegedly being obvious over Van Bree et al in view of Amalfitano et al. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The fundamental failings of Van Bree et al are detailed above. Amalfitano et al also fails to teach the required replacement of the leader sequence of human GAA with a secretory signal sequence.

In rejecting the claims as obvious, the Examiner makes reference to the paragraph beginning at line 13 on page 22 of Amalfitano et al. The referenced portion of the citation indicates that an adenovirus vector can be used to infect a cell in culture to produce a polypeptide of interest, lysosomal acid α-glucosidase is given as an example (at page 28, to which the

Examiner also refers, reference is made to human GAA). While the Examiner cites pages 3-41 of Amalfitano et al generally and, especially, pages 6, 7, 12, 22, 26, 28-30, 35 and 41, and Examples 1, 4, 9 and 13, the Examiner fails to indicate where Amalfitano et al teaches replacing the leader sequence of native human GAA with a secretory signal sequence, as required by claim 1. Indeed, in withdrawing the rejection of the claims as anticipated by Amalfitano et al, the Examiner effectively acknowledges that the reference includes no such teaching. Thus, combining Van Bree et al with Amalfitano et al would not have brought one skilled in the art any closer to the claimed invention.

Reconsideration is requested.

Claims 3, 4, 73, 75, 77 and 79 stand rejected under 35 USC 103 as allegedly being obvious over Van Bree et al, Amalfitano et al in view of Heus and Haseltine et al. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The deficiencies of Van Bree et al and Amalfitano et al are discussed above.

As pointed out previously, the present invention results, at least in part, from studies designed to test the hypothesis that chimeric lysosomal polypeptides containing an alternative signal peptide could increase the secretion of lysosomal polypeptides from transduced cells and enhance receptor-mediated uptake of lysosomal polypeptides in tissues. The data presented in the application (and in Sun et al, Mol. Ther. 14:822 (2006) – of record) make it clear that replacement of the lysosomal leader sequence (which targets the polypeptide to the lysosome) by a secretory signal peptide increased secretion from cultured cells (see, for example, Fig. 15 of the application). Furthermore, receptor mediated uptake of the chimeric polypeptide occurred efficiently (see, for example, Table 1 of Sun et al, Mol. Ther. 14:822 (2006)). The uptake was

inhibited by mannose-6-phosphate thereby implicating the involvement of mannose-6-phosphate receptors.

As discussed above, neither Van Bree et al nor Amalfitano et al teach replacement of the leader sequence of native human GAA with a secretory signal sequence. Nothing in the teachings of Heus relating to 3' untranslated region sequences of GAA or in Haseltine et al's teaching of the albumin signal sequence provide such a teaching.

Applicants again submit that it is only with hindsight that the cited references would have been combined - the documents themselves do not suggest their combination. The rejection is clearly not well founded and withdrawal of same is requested.

Claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75, 77 and 79-82 stand rejected under 35 USC 103 as allegedly being obvious over Van Bree et al, Amalfitano et al, Heus, Haseltine et al and further in view of Martin et al.. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The deficiencies of Van Bree et al and Amalfitano et al are discussed above. Nothing in the teachings of Heus relating to 3' untranslated region sequences of GAA, in Haseltine et al's teaching of the albumin signal sequence or in Martin et al's teaching of an erythropoietin signal peptide would have cured the fundamental failings of Van Bree et al and Amalfitano et al. In addition, the documents cited here, like those cited above, would only have been combined by one having benefit of the present invention. Reconsideration is requested.

Claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 stand rejected under 35 USC 103 as allegedly being obvious over Van Bree et al, Amalfitano et al, Heus, Haseltine et al, Martin et al and further in view of Whitfeld et al.. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The failings of Van Bree et al and Amalfitano et al are detailed above. As pointed out in connection with the prior rejection, nothing in the teachings of Heus relating to 3' untranslated region sequences of GAA, in Haseltine et al's teaching of the albumin signal sequence or in Martin et al's teaching of an erythropoietin signal peptide would have cured those failings, likewise, nothing in Whitfeld et al's teachings relating to a therapeutic polypeptide comprising an α-1-antitrypsin secretory signal sequence. Reconsideration is requested.

Claims 1-5, 8-12, 14-16, 18, 21, 22, 24-29, 73, 75-77 and 79-82 stand rejected under 35 USC 103 as allegedly being obvious over Van Bree et al, Amalfitano et al, Heus, Haseltine et al, Martin et al, Whitfeld et al and further in view of Meulien. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The deficiencies of Van Bree et al and Amalfitano et al are described above. It is also pointed out above that nothing in Heus, Haseltine et al, Martin et al or Whitfeld et al would have suggested replacing of the leader sequence of native human GAA with a secretory signal sequence. Indeed, the Examiner does not contend otherwise. Meulien's teaching of a Factor IX secretory signal sequence certainly would not have provided such a suggestion.

Applicants submit that the documents cited here, like those cited above, would only have been combined by one having benefit of the present invention. Reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

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Respectfully submitted,

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